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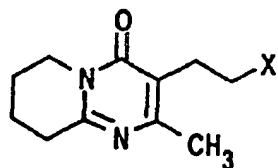
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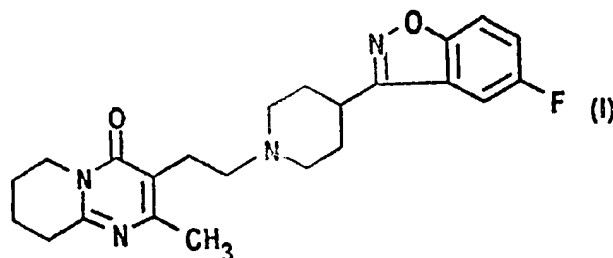
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(54) Title: A PROCESS FOR THE PREPARATION OF ANTI-PSCHOTIC 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one



(IIB)



(I)

(57) Abstract: A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of formula (IIB) where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, an intermediate in the synthesis of the anti-psychotic risperidone. The process comprises hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100 °C in the presence of a metal catalyst and the product is isolated. A process for the preparation of risperidone of formula (I) comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one with 6 fluoro-3-(4-piperidinyl)-1, 2-benzosoxazolein water in the presence of an inorganic base at 25 - 100 °C and the product is isolated.

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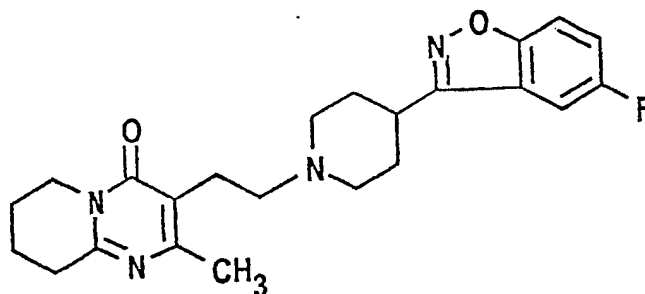
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TITLE OF INVENTION

A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidiny]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Technical field

The above compound is commonly known as risperidone and is of the formula I:

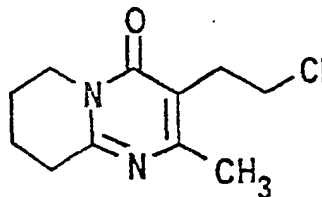


Formula I

Risperidone elicits its action by antagonising serotonin. Risperidone is a highly potent drug used in the treatment of schizophrenic states and also shows broader applications in other areas of psychosis.

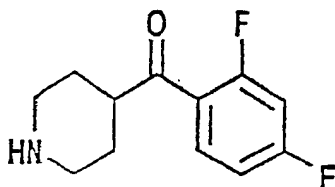
Background Art

Risperidone of the formula I is known to be prepared by the condensation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula IIA:



Formula IIA

with 4-(2,4-difluorobenzoyl) piperidine of the formula III:



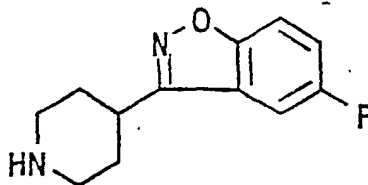
Formula III

in organic solvent such as methylene dichloride, acetonitrile, N,N-dimethyl formamide (DMF) or N-methyl pyrrolidone in the presence of an inorganic base such as sodium hydroxide, carbonate or bicarbonate at 50-100°C, followed by oximation and cyclisation (Spanish Patent No 2,050,069).

Inorganic bases used in the above reaction being sparingly soluble in organic solvent used as medium for the reaction, they may not neutralise the acid by-product fast with the result that the neutralisation may be sluggish. Due to the slow removal of the acid by-product from the reaction mixture, there are chances of decomposition of the condensation product, thereby reducing the yield and purity thereof. The yield of condensation product obtained by this condensation process is low of the order of 63.1%. This process is therefore inefficient and uneconomical. The medium for the condensation being organic, isolation of the condensation product is to be carried out by quenching the reaction mixture with water followed by extraction with organic solvent such as methylene dichloride. Solvent extraction is cumbersome, lengthy and time-consuming and also engenders poor recovery of organic solvent used for the reaction. Also organic solvents such as DMF are reported to decompose in the presence of inorganic bases at elevated temperatures (Encyclopedia of Chemical Technology, 3rd edition, 11, 263) further complicating isolation. Besides, use of organic solvents as medium for the reaction makes the process further expensive and uneconomical. Moreover, solvents such as DMF are hazardous and pollute

environment when used in large scale and also entail effluent disposal/treatment problems.

Risperidone of the formula I may also be prepared by the condensation of chlorotetrahydro pyridopyrimidine of the formula IIA with 6-fluoro-3-(4-piperidiny)-1,2-benzisoxazole of the formula IV:

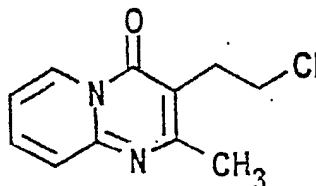


Formula IV

in an organic solvent such as DMF, 4-methyl-2-pentanone, benzene, ethanol, 1,4-dioxane, tetrahydrofuran, nitrobenzene or 1-methyl-2-pyrrolidinone in the presence of an organic base such as N,N-diethylethanamine, 4-ethyl morpholine or N-(1-methylethyl)-2-propanamine or an inorganic base such as sodium or potassium carbonate, sodium hydrogen carbonate or sodium methoxide, hydroxide or hydride, usually at 85 - 90°C (US Patent No 4804663). The organic bases which may be used in the above condensation are expensive and their use makes the above reaction uneconomical. Inorganic bases when used in organic solvent medium may result in decomposed condensation product as earlier discussed. The yield of the product obtained by this method is low of the order of 46% and renders the process inefficient and uneconomical. The reaction medium being organic, the isolation of the condensation product is to be carried out by quenching the reaction mixture with water followed by filtration of the resulting solid and recrystallisation thereof from an organic solvent such as DMF. This isolation procedure besides being cumbersome, suffers from poor solvent recovery. Also due to use of inorganic bases in organic solvent such as DMF, isolation

becomes further complicated for reasons as explained earlier. Organic solvents used as reaction medium further makes the process expensive and uneconomical. Also this process is not free from the disadvantages due to use of solvents such as DMF as aforesaid.

The intermediate chloro tetrahydro pyridopyrimidine of the formula IIA in the synthesis of anti-psychotic risperidone of the formula I may be obtained by hydrogenation of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula VA:

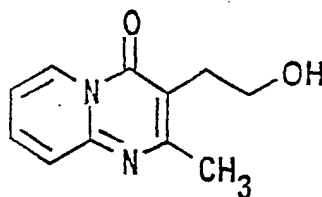


Formula VA

in acetic acid medium at 50 psi and at 25-30°C in the presence of Pd/C catalyst. (A Thesis entitled "Synthesis of Drugs & Drug Intermediates" submitted to "The University Of Mumbai" by Ms Evelyn D Lobo, p35, June 1996, for the degree of M Pharm Sci.). This hydrogenation may produce predominantly dechlorinated compounds as by-products, since dechlorination may be accelerated in acetic acid medium. This may result in low yield and purity of the product. The yield of the product obtained by this method is low of the order of 77%, thus making this process inefficient and uneconomical. The isolation of the product involves filtration of the catalyst followed by evaporation of acetic acid from the reaction mixture, dissolving the resulting residue in a solvent, deacidification and evaporation of solvent followed by recrystallisation of the resulting solid from 2-propanol. Such multiple steps for isolation are cumbersome, lengthy and time consuming. Acetic acid is a hazardous and flammable solvent and pollutes the environment when used in

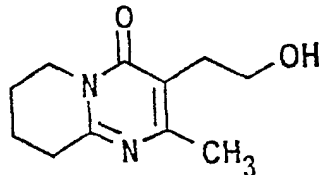
large scale. Also its use makes the process expensive and further uneconomical.

The chloro tetrahydro pyridopyrimidine reactant of the formula IIA may also be prepared by hydrogenation of the 3-(2-hydroxyethyl)-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula VI:



Formula VI

using Pd/C catalyst in aqueous ethanol at 25 - 30°C followed by reacting the resulting hydroxyethyl tetrahydro pyridopyrimidine compound of the formula VII :



Formula VII

with thionyl chloride in methylene chloride at 25-30°C for 24 hours (Spanish Patent No 2,050,069). This route involves two steps for the preparation of the compound of the formula IIA and is lengthy and time-consuming. Moreover, thionyl chloride is hazardous and when used in large scale, pollutes the environment. The overall yield of the product obtained by this method is low of the order of 44% due to two moderately yielding steps, thus making the process inefficient and uneconomical.

An object of the invention is to provide a process for the preparation of risperidone of the formula I, which is simple and less time consuming.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is inexpensive and economical.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which results in high yield and purity of risperidone and is efficient.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is safe and does not pollute the environment.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is commercially feasible.

Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which is simple and less time consuming.

Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which is inexpensive and economical.

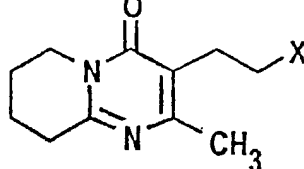
Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which results in high yield and purity of tetrahydro pyridopyrimidine and is efficient.

Another object of the invention is to provide a process for the preparation of chlorotetrahydro pyridopyrimidine of the formula IIB, which is safe and does not pollute the environment.

Another object of the invention is to provide a process for the preparation of chlorotetrahydro pyridopyrimidine of the formula IIB, which is commercially feasible.

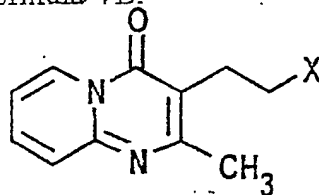
Disclosure of the invention

According to the invention there is provided a process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula IIB:



Formula IIB

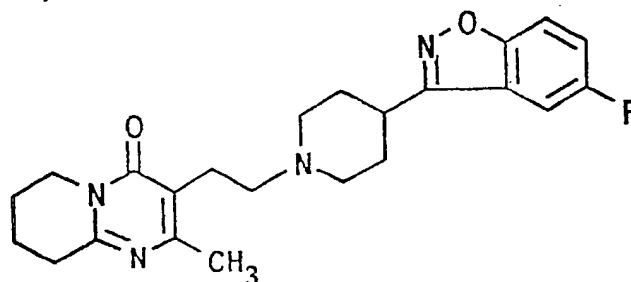
where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, comprising hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula VB:



Formula VB

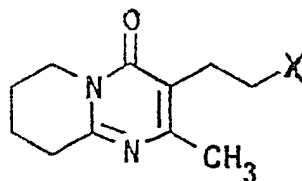
in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100°C in the presence of a metal catalyst followed by isolation of the resulting product.

According to the invention there is also provided a process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



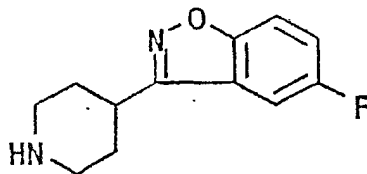
Formula I

comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-one of the formula IIB:



Formula IIB

where X may be halo, acyloxy or sulfonyloxy such as tosyloxy or mesyloxy, with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole of the formula IV:



Formula IV

in water in the presence of an inorganic base at 25 - 100°C followed by isolation of the resulting product.

The compound of the formula IIB is an intermediate in the synthesis of the anti-psychotic risperidone.

The term halo includes chloro, bromo or iodo. Preferably X may be chloro.

The pyridopyrimidine compound of the formula VB may be prepared in known manner. (A thesis entitled "Synthesis of Drugs and Drugs Intermediates" submitted to "The University of Mumbai" by Ms Evelyn D Lobo, p 30, June 1996, for the degree of M Pharm Sci.).

The inorganic acid in the aqueous medium for the hydrogenation may be sulfuric acid, hydrochloric acid or hydrobromic acid, preferably hydrochloric acid. The inorganic acid solubilises the pyridopyrimidine

compound of the formula VB in aqueous medium by converting it to its water soluble salt, prior to hydrogenation.

The metal catalyst may be platinum, palladium, nickel, rhodium or ruthenium supported on solid support such as calcium carbonate, alumina, barium sulfate, silica or activated carbon. Preferably palladium supported on activated carbon may be used.

Preferably the reduction temperature may be 25 - 40°C.

Preferably the hydrogenation is carried out at pressure of 25 psi.

The isolation of the tetrahydro pyridopyrimidine of the formula IIB may be carried out by filtration of the metal catalyst followed by pH adjustment to 4 - 10 of the resulting mixture with a base such as an alkali metal hydroxide or carbonate. The resulting solid is then filtered at 0 - 50°C, preferably at 10 - 20°C. Alternatively the filtrate after removal of catalyst, may be directly subjected to insitu condensation with the compound of the formula IV to produce risperidone.

The benzisoxazole compound of the formula IV may be prepared in known manner (US Patents Nos 4,355,037 and 4,804,663).

The inorganic base used in the condensation may be an alkali metal carbonate such as sodium, potassium or lithium carbonate or sodium bicarbonate or an alkaline earth metal carbonate such as calcium, barium or strontium carbonate or an alkali metal hydroxide such as sodium, potassium or lithium hydroxide or an alkaline earth metal hydroxide such as calcium, barium or strontium hydroxide. Preferably sodium carbonate may be used.

The condensation temperature may be preferably 60 - 90°C.

The isolation of risperidone from the reaction mixture is carried out by filtration at 25 - 40°C followed by purification, preferably by crystallisation using organic solvents such as DMF or N,N-dimethyl acetamide

or C₁₋₃ aliphatic alkanol or ether such as diethyl ether or diisopropyl ether or tetrahydrofuran or ketone such as 2-propanone, 2-butanone or 4-methyl-2-pentanone, preferably DMF.

The process of the invention for the preparation of the tetrahydro pyridopyrimidine of the formula IIB is carried out in aqueous medium because of which it proceeds at a controlled rate. Therefore dechlorination of the compound of the formula IIB when X is chloro, is prevented. The process of the invention results in high yield (83%) and purity (99%) of the product of the formula IIB and is efficient and economical. The tetrahydro pyridopyrimidine compound of the formula IIB is obtained from a single step reaction and eliminates multiple steps for isolation as described in the prior art. The procedure to isolate the product of the formula IIB obtained by the process of the invention comprises filtration of the catalyst, pH adjustment and filtration of the resulting solid, and is therefore simple, less cumbersome, less tedious and less-time consuming when compared to the prior art methods. The compound of the formula IIB when subjected to insitu condensation makes the process for the preparation of risperidone further less time-consuming and economical. The process also eliminates hazardous solvents and pollution of the environment caused thereby and is safe to carry out. The use of water instead of organic solvents as medium for the reaction makes the process further inexpensive and economical and also eliminates solvent recovery/disposal/treatment problems as in the prior art. Due to the above reasons, this process is also commercially feasible.

According to the invention the process for the preparation of risperidone is carried out in an aqueous medium in the presence of an inorganic base. The solubility of the inorganic base in the aqueous medium

being high, the neutralisation of the acid by-product formed during the condensation is fast by the inorganic base in solution form. This prevents degradation of risperidone by the acid by-product and also results in high yields (66 - 72%) and purity (~99%) thereof, thereby making the process efficient and economical. The process of the invention does not use organic bases and is inexpensive. The reaction medium being aqueous, quenching with water or extraction with organic solvents is unnecessary for isolation of risperidone. The isolation procedure involves a single step ie filtration and is therefore simple, less cumbersome and less time-consuming when compared to the prior art methods. The process eliminates use of hazardous solvents and pollution of the environment caused thereby and is safe. The use of water as medium instead of organic solvents is inexpensive and economical and eliminates solvent recovery/disposal/treatment problems as in the prior art. Due to the above reasons, the process of the invention is commercially feasible.

The following experimental examples are illustrative of the invention but not limitative of the scope thereof.

Example 1

Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula II A :-

To a 500 ml hydrogenation flask was charged 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one (20.0 g, 99% pure by HPLC analysis), water (50.0 ml), 30% HCl (10.0 ml) and 10% Pd/C (2.0 g). The contents of the flask were reduced with hydrogen gas at pressure 25 psi under agitation for 6 hours at 30°C. The catalyst in the reaction mixture was filtered through Whatmann 1 filter paper. The filtrate free from catalyst was basified

by addition of 45% caustic soda lye (6.0 ml). The product was filtered and dried.

The product obtained was characterised by Nuclear Magnetic Resonance (NMR) Spectroscopy as follows:

^1H NMR (60 MHz), CDCl_3 : δ 3.7 (m, 4H); δ 2.9 (t, $J = 6\text{Hz}$, 2H); δ 2.3 (s, 3H); δ 1.8 (m, 6H).

Yield = 16.6 g (83 %)

Purity = 99% [when analysed by High Performance Liquid Chromatography (HPLC)]

Example 2

Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Risperidone of the formula I) : -

To a 10. L flask was charged the tetrahydro pyridopyrimidine (666.0 g) of Example 1, water (3330.0 ml) and 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (639.0 g) and sodium carbonate (1152.0 g). The contents of the flask were heated to 85 - 90°C and stirred for 4 hours. The reaction mixture was cooled to room temperature and filtered. The product was purified by crystallisation from DMF.

The product was characterised by NMR spectroscopic studies as follows:

^1H NMR (60 MHz, CDCl_3): δ 7.5 - 7.9 (m, 1H); δ 6.8 - 7.45 (m, 2H); δ 3.8 - 4 (m, 2H); δ 2.45 - 3.5 (m, 11H); δ 2.35 (s, 3H); δ 1.65 - 2.25 (m, 8H).

Yield = 865.0 g (72%)

Purity = 99% (when analysed by HPLC)

Example 3

Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a] pyrimidin-4-one (Risperidone of the formula I) by one-pot reaction : -

The filtrate free from catalyst of Example 1 was neutralised by addition of 45% caustic soda lye (5.5 ml) in a 250 ml flask. To it were charged 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (19.2 g) and sodium carbonate (34.6 g). The reaction mixture was heated to 85 - 90°C for 4 hours under stirring, cooled to room temperature and filtered. The cake was purified by crystallisation from DMF.

The product was characterised by NMR spectroscopic studies as follows:

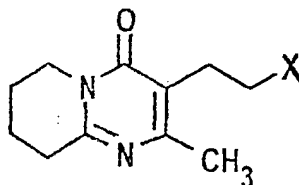
¹H NMR (60 MHz, CDCl₃) : δ 7.5 - 7.9 (m, 1H); δ 6.8 - 7.45 (m, 2H); δ 3.8 - 4 (m, 2H); δ 2.45 - 3.5 (m, 11H); δ 2.35 (s, 3H); δ 1.65 - 2.25 (m, 8H).

Yield = 30.0 g (72%)

Purity = 99% (when analysed by HPLC)

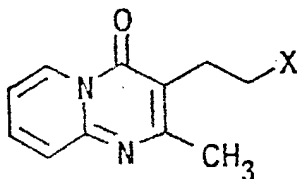
CLAIMS

- 1) A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula IIB:



Formula IIB

where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, comprising hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one of the formula VB:

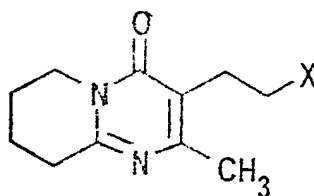


Formula VB

in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100°C in the presence of a metal catalyst followed by isolation of the resulting product.

- 2) A process as claimed in claim 1, wherein X is chloro.
- 3) A process as claimed in claim 1 or 2, wherein the hydrogenation is carried out at pressure of 25 psi.
- 4) A process as claimed in any one of claims 1 to 3, wherein the inorganic acid is hydrochloric acid.
- 5) A process as claimed in any one of claims 1 to 4, wherein the hydrogenation is carried out at 25 - 40°C.
- 6) A process as claimed in any one of claims 1 to 5, wherein the metal catalyst is palladium supported on activated carbon.

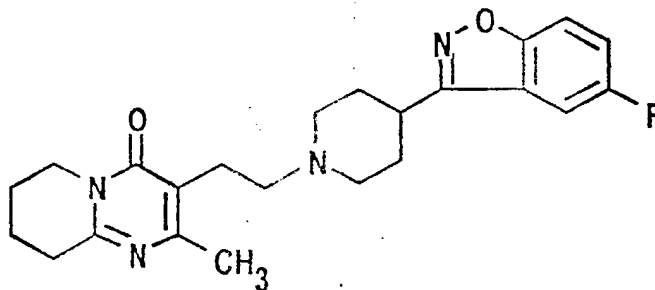
7) A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

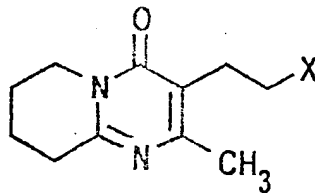
where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, substantially as herein described particularly with reference to Example 1.

8) A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



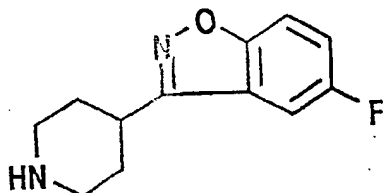
Formula I

comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

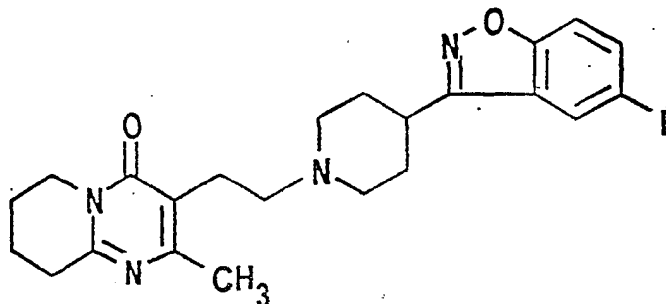
where X may be halo, acyloxy or sulfonyloxy such as tosyloxy or mesyloxy, with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole of the formula IV:



Formula IV

in water in the presence of an inorganic base at 25 - 100°C followed by isolation of the resulting product.

- 9) A process as claimed in claim 8, wherein X is chloro.
- 10) A process as claimed in claim 8 or 9, wherein the inorganic base is sodium carbonate.
- 11) A process as claimed in any one of claims 8 to 10, wherein the condensation is carried out at 60 - 90°C.
- 12) A process as claimed in any one of claims 8 to 11, wherein the purification during isolation is carried out by crystallisation from DMF.
- 13) A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



Formula I

substantially as herein described particularly with reference to Examples 2 and 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 00/00053

CLASSIFICATION OF SUBJECT MATTER IPC⁷: C07D 471/04, 498/04 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC⁷: C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CA, REGISTRY, WPI, EPODOC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ES 2074966 A1 (VITA-INVEST, S.A., SPAIN) 16 September 1995 (16.09.95) the whole document.	1-13
A	ES 2050069 A1 (VITA-INVEST, S.A., SPAIN) 1 May 1994 (01.05.94) the whole document. (cited in the application)	1-13
A	US 4957916 A (JANSSEN PHARMACEUTICA N.V., BELG.) 18 September 1990 (18.09.90) examples 4,8.	1-13
A	EP 0196132 A2 (JANSSEN PHARMACEUTICA N.V., BELG.) 1 October 1986 (01.10.86) example 5. (cited in the application)	1-13
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 12 September 2000 (12.09.2000)		Date of mailing of the international search report 29 March 2001 (29.03.2001)
Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535		Authorized officer MÜLLER-HIEL Telephone No. 1/53424/434

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A2	196132	01-10-1986	AT	E	79379	15-08-1992
EP	A3	196132	20-01-1988	AU	A1	55297/86	02-10-1986
EP	B1	196132	12-08-1992	AU	B2	579232	17-11-1988
				BG	B2	60432	31-03-1995
				CA	A1	1256867	04-07-1989
				CN	A	86101906	01-10-1986
				CN	B	1022566	27-10-1993
				CS	A3	9103822	13-05-1992
				CY	A	1801	17-02-1995
				CZ	B6	280767	17-04-1996
				DE	C0	3686341	17-09-1992
				DE	T2	3686341	14-01-1993
				DK	A0	1439/86	26-03-1986
				DK	A	1439/86	28-09-1986
				DK	B1	168537	18-04-1994
				ES	A1	553419	16-05-1987
				ES	A5	553419	15-06-1987
				ES	A1	8705081	01-08-1987
				FI	A0	861328	26-03-1986
				FI	A	861328	28-09-1986
				FI	A	893001	19-06-1989
				FI	A0	893001	19-06-1989
				FI	B	81800	31-08-1990
				FI	C	81800	10-12-1990
				GR	A	860800	21-07-1986
				HK	A	1087/94	14-10-1994
				HU	A2	42461	28-07-1987
				HU	B	195793	28-07-1988
				IE	B	58388	08-09-1993
				IL	A0	78250	31-07-1986
				IL	A1	78250	12-05-1991
				JP	A2	61221186	01-10-1986
				JP	B4	6013511	23-02-1994
				KR	B1	9100165	21-01-1991
				KR	B1	9100437	25-01-1991
				LT	A3	2071	15-06-1993
				LU	A9	88576	21-03-1995
				LV	A4	5778	20-12-1996
				LV	B4	5778	20-06-1997
				NO	A	861230	29-09-1986
				NO	B	162765	06-11-1989
				NO	C	162765	14-02-1990
				NZ	A	215462	29-09-1988
				PH	A	24016	09-02-1990
				PT	A	82254	01-04-1986
				PT	B	82254	21-04-1988
				SG	A	1192/94	17-03-1995
				SK	B6	280125	06-08-1999
				SU	A3	1468419	23-03-1989
				ZA	A	8602279	25-11-1987
				US	A	4804653	14-02-1989
ES	AA	2050069	01-05-1994	ES	UA	1021124	01-09-1992
ES	BA	2050069	16-12-1994	ES	YA	1021124	16-03-1993
ES	AA	2074966	16-09-1995	ES	UA	1026972	16-06-1994
ES	BA	2074966	16-06-1996				
US	A	4957916	18-09-1990	AT	E	122348	15-05-1995
				AU	A1	39171/89	08-03-1990
				AU	B2	619877	06-02-1992
				CA	A1	1331609	23-08-1994
				CN	A	1040194	07-03-1990
				CN	B	1023602	26-01-1994
				DE	C0	68922537	14-06-1995
				DE	T2	68922537	14-09-1995
				DK	A0	3836/89	04-08-1989
				DK	A	3836/89	06-02-1990
				EP	A2	353821	07-02-1990
				EP	A3	353821	17-07-1991
				EP	B1	353821	10-05-1995
				ES	T3	2074462	16-09-1995
				FI	A0	893701	04-08-1989
				FI	A	893701	06-02-1990
				FI	A	923128	07-07-1992
				FI	A0	923128	07-07-1992
				FI	B	90238	30-09-1993
				FI	C	90238	10-01-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN 00/00053

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		FI B1 103406	30-06-1999
		HU A2 55385	28-05-1991
		HU B 206341	28-10-1992
		IE B 66198	13-12-1995
		IL A0 91194	19-03-1990
		IL A0 105594	22-09-1993
		IL A1 91194	12-04-1994
		IL A1 105594	07-10-1994
		JP A2 2088572	28-03-1990
		JP B2 2779216	23-07-1998
		KR B1 145706	17-08-1998
		NO A0 893168	04-08-1989
		NO A 893168	06-02-1990
		NO B 176051	17-10-1994
		NO C 176051	25-01-1995
		NZ A 230045	27-11-1990
		PH A 26550	19-08-1992
		PT A 91364	08-03-1990
		PT B 91364	31-03-1995
		SU A3 1687030	23-10-1991
		ZA A 8905978	24-04-1991
		US A 5015740	14-05-1991

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